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THE STATE OF GENETICS

Last summer the geneticists of many lands gathered for a week on Long Island. Their discussions reflected the ferment of a science that is changing both itself and the other provinces of biology

by A. Buzzati-Traverso

IF THE vitality of a science can be measured by the number of facts it brings to light, or by the novelty of its hypotheses, or by the changes in its subject matter, then the science of genetics is extraordinarily vital at present. Two dominant processes are currently at work in this science. On the one hand some earlier genetic findings are being subjected to a more refined analysis; this demonstrates more and more clearly the great complexity of the genetic mechanism, and leads to a reconsideration of older genetic concepts. On the other hand genetic ideas and methods are revolutionizing other biological sciences. These ideas and methods show that the most diverse phenomena which occur in living matter can be regarded as expressions of fundamental processes which are similar throughout the living world. The divisions of biology, such as botany, zoology, bacteriology, embryology and biochemistry, are accordingly breaking down; as a result of genetic investigations we recognize unexpected links among the biological disciplines. Genetics is a kind of cement that joins the many biological phenomena and gives them unity and meaning.

These new trends, these signs of a profound transformation in biology, were much in evidence at a recent scientific meeting. The meeting was the Sixteenth Symposium on Quantitative Biology held by the Long Island Biological Association in Cold Spring Harbor, N. Y., from June 7 to June 15. The title of the meeting was "Genes and Mutations," two words which describe the pivotal elements of biological inheritance. More than 150 biologists, chemists and physicists convened in the congenial environment of the Carnegie Institution at Cold Spring Harbor. Listed in the program were the names of more than 40 of the world's leading geneticists. American, British, Danish, French, Italian, Swedish, Swiss and Yugoslav research workers lived for nine days from early in the morning until late at night in an atmosphere of inquiry and understanding. The result was a series of exciting and fruitful discussions.

What were the themes of the meeting that reflected the state of genetics? What are the most representative and important trends in this science?

The answer is not easy to give, and it will inevitably reflect the personal outlook of the writer. To summarize in a few sentences the discussions at Cold Spring Harbor is almost impossible. The main trends of the meeting can nevertheless be outlined.

GENETICS has been defined as the science that studies heredity and variation. But every phenomenon of biology falls within these limits; each event in the life history of a plant or animal can be explained in terms of inherited traits and their relation to environmental conditions. A horse begets horses and not butterflies because certain physical elements are transmitted from parents to offspring through the germ cells. This fact insures the maintenance of the chief characteristics of the species. But each horse is different from every other horse because the germ cells can also transmit a vast array of different characteristics. These inherited differences maintain the genetic plasticity of the species which is necessary for its survival under different environmental conditions. It is this hereditary variability that is used by man to select races of domestic animals or cultivated plants suited to his needs. Genetics is concerned with the phenomena that underlie such realities. But despite the range of its work, genetics has long been considered a specialized and limited biological subject. How did this impression arise?

For many years geneticists worked hard to get a clear picture of the main laws of inheritance. In this effort they concentrated upon a small number of organisms. To an outside observer it often appeared that the regularities of inheritance observed by geneticists applied in only a few cases, such as the fruit fly *Drosophila*, corn or mice. During this early period of intense investigation geneticists were compelled to coin new words to describe new phenomena; the result was the evolution of a rather specialized language. Other biologists could not make much out of this jargon, and for a time there was a cleavage between genetics and other biological disciplines.

During this period, however, the geneticists made remarkable progress. They found that heredity is controlled by individual particles, composed of proteins and nucleic acids, which are transmitted by both parents to their offspring. Such particles, the genes, do not blend, and do not contaminate one another. The hereditary constituents of the parents can therefore be reassorted in different ways in different individuals at each generation. The genes are located in well-defined bodies, the chromosomes, which lie in the nucleus of every cell in an organism. The genes are arranged in the chromosomes in linear order. Owing to the amazing regularity of the process by which a cell divides into two daughter cells, the chromosomes are also equally divided and distributed. When the sperm and egg cells are formed, and when they are joined, the genes are transmitted and recombined from one generation to the next according to precise quantitative laws. It is these laws that Gregor Mendel discovered in the garden pea around 1860. The geneticists of this century have been able to show that the regularities of inheritance which Mendel discovered are due to the dance of the chromosomes and the genes, a dance that can be observed by the human eye with the help of a microscope. This discovery of the genetic basis of inheritance was the first synthesis of different biological fields. Before that time the study of the cell and the structure of living organisms proceeded along separate and to some extent diverging pathways; the chromosome theory of heredity showed that these apparently unrelated phenomena were due to a common cause related to the process of cell reproduction. The first important step had been made, and the others were bound to follow.

The hypothesis of the linear arrangement of genes within the chromosomes was originally proposed to account for the facts observed in cultures of fruit flies. It was later found to be true for other organisms as well. The basic mechanism of cell division and heredity was found to be common to both animals and plants, and although their structure, function and life history seemed to show more differences than similarities, the transmission of these traits from one generation to the next was found to be the result of the same genetic mechanism.

Once this was established, it was possible to explain the differences among organisms in terms of differences among the genes and their action. Moreover, the stupendous transformations that have occurred in organisms during the course of evolution could be explained by means of transformations of the genes. Finally, if the genes were the fundamental reproducing particles, and were responsible for the development of all the traits exhibited by every organism, then we must regard the gene as the fundamental biological element, as the very basis of life. The extraordinary fact is this: that the ideas presented in these last few sentences are not mere speculations but to a large extent have been proved by experiments.

At Cold Spring Harbor we heard the latest developments in these ideas. Until a short time ago, for example, the chromosome theory of heredity, which had been instrumental in bringing about the scientific unification of plants and animals, did not seem to hold true for the lower organisms such as bacteria and viruses. But the recent genetic attack on the problem of bacterial variation has changed the situation. True inherited variations have been found in bacteria and have proved to be comparable to the mutations found in the genes of higher organisms. Similar results have been obtained in bacteriophages, the viruses which act as parasites of bacteria. At the meeting some startling new discoveries in this field were announced. Edward D. DeLamater of the University of Pennsylvania described convincing evidence for the existence of chromosomes and their regular division in bacteria. He showed clear photographs and microscope slides of cell division in *Bacillus megatherium* which make it possible for the first time to regard bacterial cells as having a structure similar to that of other cells. DeLamater also presented evidence for the existence of fusion processes between bacterial cells; this may prove to be the first microscopic evidence of sexual reproduction in such organisms.

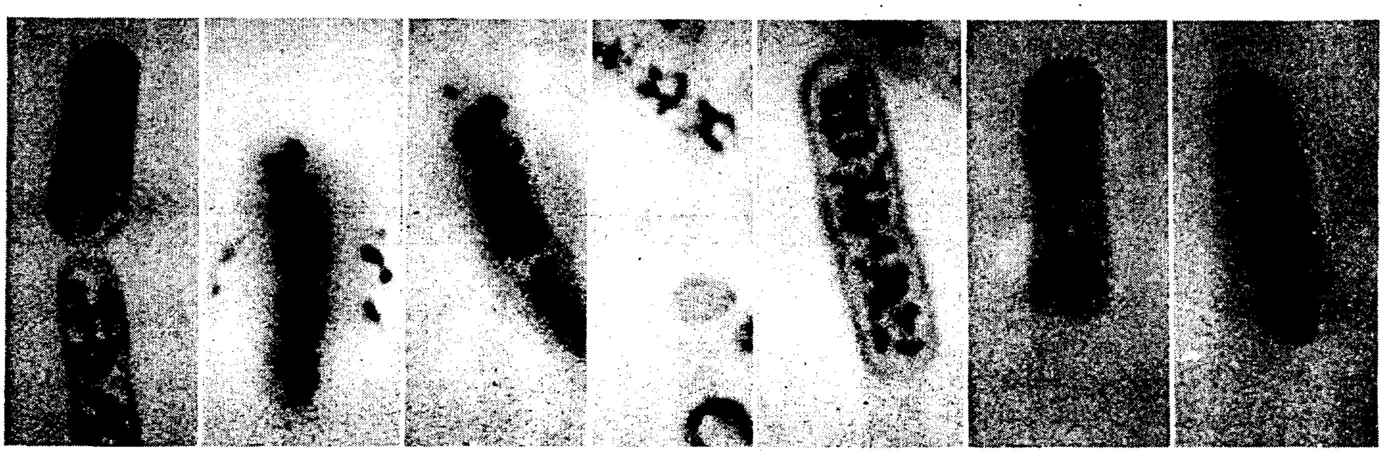
Five years ago Joshua Lederberg of the University of Wisconsin had discovered that bacteria were capable of combining their genes; at Cold Spring Harbor he reported still further evidence of this behavior, and showed how complicated the genetic mechanism of such a common bacterium as the colon bacillus, *Escherichia coli*, can be. Today our genetic understanding of the bacterial cell is in much the same state of change as our knowledge of higher plants and animals was 40 years ago. Then, as now, the evidence for the linear arrangement of genes in the chromosomes was found first by the breeding of experimental organisms, while the visible proof had to wait a number of years. We may well be on the verge of still other developments in this significant field of genetics.

Lederberg also presented evidence for the existence of curious small forms of the bacterium *Salmonella typhi murium*. When passed through a filter that holds back the larger bacteria, these forms retain their genetic individuality. They may well be the first specialized sex cells to be observed in this group of organisms. Although bacterial cells are tiny, the biologist has always hoped that their structure would be revealed by improved techniques; now this structural exploration would seem to have been started by genetics.

On the other hand, bacteriophages are obviously smaller than the bacteria on which they prey; it seems doubtful that we shall ever perceive their chromosomes. In spite of this, these minute organisms certainly possess genetic mechanisms very similar to those in higher forms. At Cold Spring Harbor A. D. Hershey of Washington University showed how it is possible to construct maps which indicate the spatial relationships between several genes in the bacteriophage that disintegrates *Escherichia coli*. S. E. Luria of Indiana University developed a very stimulating hypothesis of how bacteriophages reproduce and mutate. Finally, at a still lower level of genetic organization, Harriett Ephrussi-Taylor of the Institute of Genetics in Paris showed that it is possible to recognize several genetic units within an *extract* of the pneumococcus. The extract contains nucleic acid from one strain of this bacterium; when the extract is added to a culture of another strain, the genetic constitution of the latter is transformed.

So much the same genetic mechanism would seem to be common to all living things; all would appear to share a master plan. This is true of reproducing units so primitive as to lack many characteristics we commonly associate with life, of viruses that lie far below the resolving power of the light microscope, of bacteria that until recently seemed to lack the organized nuclei of other cells, of one-celled animals and plants, and of many-celled organisms including man.

A complete genetic account of life requires that we explain the way genes control the development of the various structural and functional traits of any organism. At Cold Spring Harbor a new light was cast on this area. N. H. Horowitz of the California Institute of Technology and David M. Bonner and Norman H. Giles of Yale University showed how individual genes are responsible for individual biochemical reactions. According to the so-called "one gene-one function" hypothesis it has been surmised that in the course of the development of an organism each gene

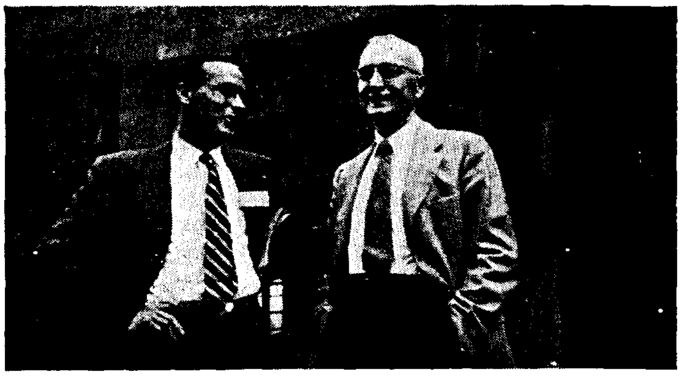


CHROMOSOMES OF BACTERIA, which until recently were not known to exist, were exhibited at Cold Spring Harbor by Edward D. DeLamater of the University of Pennsylvania. The bacterium is *Bacillus megatherium;* the chromosomes are the dark bodies within it. The stages shown here run from prophase to interphase.

Szilard, Bonner

Buzzati, Hadorn, Goldschmidt

McClintock, Lindegren



Giles, Kaufmann

serves as a model from which specific kinds of enzyme proteins are copied; these enzyme proteins in turn act as catalyzers or pacemakers of the chemical reactions that take place in the cell. The red bread mold *Neurospora* has provided much precious evidence for the validity of this hypothesis. The Caltech and Yale investigators have analyzed the inherited ability of many strains of this mold to synthesize specific enzymes. Although the one gene-one enzyme relation seems to hold true in some cases, in others it does not; the underlying mechanism would seem to be more complicated than the hypothesis suggests. The interest of such studies, however, goes far beyond the analysis of particular chemical reactions. The genetic approach to the problem of biological synthesis, of how an organism transforms the substances it absorbs from its environment into living matter, has produced a remarkable change in the science of biochemistry. Until a short time ago this science was concerned chiefly with problems of catabolism, of how substances such as sugars or fats or proteins were broken down by the organism. Since biochemistry has become linked with genetics it has become more and more concerned with the problem of anabolism, of synthesis. By this token biochemistry is now closer to the general problems of biology.

THE impact of genetics has been felt not only in other specialized fields of biology but also in the most general biological approach: the study of evolution. After Charles Darwin developed his general theory on the origin of species by means of natural selection, and the biologists and paleontologists of the 19th century provided overwhelming evidence for the occurrence of evolution in past eras, it seemed for some decades that evolutionary studies had come to a dead end. It seemed doubtful that any biologist in one lifetime could prove experimentally the theories that would best interpret the observed evolutionary facts. The process of evolution has required hundreds of millions of years to produce the great variety of living animals and plants; the biologist can only study the changes that occur within his time, at the very most a few decades. But as soon as genetics had formulated the chromosome theory of inheritance, and had shown that hereditary changes are due to mutations in the gene or in the chromosome, a new line of attack on the problem of evolution was disclosed. Evolutionary changes were found to occur within a few generations as the result of the effects of natural selection on a vast array of mutations. This provided a stimulus for the study of mutation itself. The study of mutation by its artificial induction has been an important part of genetics ever since. The occurrence of spontaneous mutations in plant populations was discussed at Cold Spring Harbor by the Swedish geneticist Ake Gustafsson; it was shown that single mutations may have a remarkable evolutionary importance. At the same time, a new approach to the problem of measuring the rate of spontaneous mutation was presented by Aaron Novick and Leo Szilard of the University of Chicago.

The Chicago investigators grow vast populations of bacteria in a new apparatus called the chemostat. In this apparatus it is possible to regulate the rate at which nutrients are fed the bacteria and therefore the rate of their reproduction. By this method it has been shown that the rate of spontaneous mutations is related to astronomical time and not to the number of generations occurring within a period of time. How this may affect our evolutionary theories is not yet clear, because we have no evidence on this point for higher forms of life. However, some experimental evidence presented at the Symposium showed that, contrary to what has been generally believed, an increase in the mutation rate may bring about a more rapid evolutionary change. We now know of several physical and chemical agents capable of increasing the mutation rate in every organism, and several papers presented at the meeting offered new evidence as to how the various agents may act and how different organisms may react to the same agent.

THE genetic attack on biological problems proceeds on an ever-widening front, and it becomes increasingly difficult for the geneticist to keep abreast of new genetic information. This progress is not only quantitative; it is

Horowitz, Atwood, Lederberg

Novick, Rubin

Stadler, Hollaender, Stone

Davis, Demerec

also qualitative. Not only is a wider range of organisms being analyzed in genetic terms, and the genetic background of many different biological phenomena being found, but also the very study of fundamental genetic processes is being pursued at deeper and deeper levels. As in other sciences, the accumulation of new experimental facts makes previous theoretical interpretations obsolete, and new hypotheses are required to account for both the new and the old facts. In genetics we are presently witnessing a very interesting process of refinement of the old fundamental concepts of our science. The experimental evidence now coming from a deeper study of heredity in some of the classical organisms, such as *Drosophila* and corn, as well as to the newcomers to the laboratories of inheritance, such as bacteria and other microorganisms, requires that the geneticist continuously revise his fundamental concepts.

This process of shifting ideas, this change of key, was quite evident in the papers and discussions of the Cold Spring Harbor meeting. The *prima donna* was the gene itself. Originally the gene was conceived as a tiny fraction of the chromosome which controlled a single hereditary trait and had no relation to other genes; it was thought to be in an ivory tower which kept it from promiscuity with other genes and other cell constituents. Although each gene was regarded as a governing center of cell activity, there seemed to be no connection between these numerous centers. Later it was found that one gene could control more than one trait at one time, and that one trait could be affected by more than one gene. Then it was shown that sometimes a gene can change its position within the chromosome and thereby have its function altered. Meanwhile the study of the function of the gene within the cell was being developed, and it was found that the effects of the same gene differ in different cellular environments. Furthermore, the discovery that one can produce mutations with physical and chemical agents showed that the gene, being itself a cellular constituent, cannot be regarded as a completely isolated entity, but that it interacts with other genes as well as with other constituents of the cell.

Now the ivory tower has collapsed, and a more functional picture of the gene emerges. During the early development of genetics the gene was regarded as a material particle that could account for the transmission and reassortment of hereditary traits in successive generations. Then it became the particle in which mutation occurs. Finally it was thought to be the particle that plays a special role in the biochemistry of the cell. This same particle, the gene, was thus being attacked from three different angles: no wonder that the conclusions reached by the three types of attackers sometimes do not fit perfectly with one another. The same thing happens when three climbers approach the summit of a mountain from different sides: although it is the same mountain it may look very different to each climber.

In the introductory lecture of the Symposium Richard B. Goldschmidt of the University of California made the audience feel the difficulties encountered when one tries to interpret some genetic phenomena with the assumption that the genes are discrete particles having no interrelationships with neighboring genes. Barbara McClintock of Cold Spring Harbor and L. J. Stadler of the University of Missouri brought new evidence to the subject from their work with corn. These contributions pointed to the present need of regarding the activity of the gene as a function of the internal organization of the chromosome. The end result is a more elaborate concept of the constitution of the genetic material within the cell nucleus.

Two years from now the Ninth International Congress of Genetics will be held in Italy, and it is safe to make the prediction that many of these present ideas will then look obsolete. As the rate of change in living things can be taken as a good measure of evolutionary progress, the rate of change in ideas can be considered as a sign of health and vitality of a science. The outlook for genetics is good; this science surely promises a rapid evolution in our knowledge of the mechanism of heredity.

A. Buzzati-Traverso is professor of genetics at the University of Pavia in Pavia, Italy.